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EDITORIAL

Extent of Lymphadenectomy in Esophageal Cancer: How Many Lymph Nodes Is Enough?

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There is no question that presence of lymph node (LN) metastasis in esophageal cancer is one of the most powerful prognostic indicators. Multiple studies have demonstrated that patients with lymph node metastasis have more aggressive tumor biology, higher rates of locoregional and distant recurrence, and hence, worse survival. Esophageal cancer staging according to the sixth edition of the tumor–node–metastasis (TNM) staging manual of the American Joint Committee on Cancer (AJCC) uses only the location of the involved LN or the distance from the primary tumor for nodal disease staging (i.e., N1 versus M1a).[1] This method tends to group patients with very different disease burden and biologic behavior into a similar stage, resulting in a less powerful staging system. More recent studies have explored the impact of LN metastases further, and investigators seem to agree that it is not only a question of the presence or absence of nodal disease, but more importantly, how many LN are involved with disease.[2,3] Rizk and colleagues reported that the prognosis of patients after esophagectomy worsens significantly after four or more lymph nodes have metastases, irrespective of T stage.[3] LN subclassification according to nodal groupings showed differences in survival curves, and better prognostic stratification can be obtained to facilitate treatment decisions. The Worldwide Esophageal Cancer Collaboration has reported with tremendous effort an international and multi-institutional dataset that refined the recommendations for the revised esophageal cancer staging system and incorporates the important factor of extent of nodal disease.[4] After these and other studies highlighted the importance of lymph node subclassification, the upcoming seventh edition of the AJCC TNM staging manual has incorporated these changes into a more robust esophageal cancer staging system.[5] The new staging will have three groups of positive nodal disease (N1, 1–2 regional LN; N2, 3–6 regional LN; N3, more than 7 metastatic LN).[5] The need for more detailed nodal analysis now puts the pressure on performing a thorough and adequate lymphadenectomy during esophagectomy in order to ensure an accurate nodal stage, but what is the optimal extent of lymphadenectomy for esophageal cancer to ensure adequate LN clearance and avoid understaging the disease? Does a more radical lymphadenectomy confer a survival advantage, or is the improved survival an effect of stage migration? Is a more radical lymphadenectomy also necessary in cases where chemoradiation therapy is also administered?

In this issue of the *Annals of Surgical Oncology*, two manuscripts investigate the survival impact of the extent or adequacy of lymphadenectomy in esophageal squamous cell carcinoma and adenocarcinoma. The first article is a large retrospective study from China. Hu and colleagues evaluate the influence of the number of dissected LN on the accuracy of TNM staging and prognosis in esophageal squamous cell carcinoma (ESCC). This is an analysis of 1,098 patients who underwent esophagectomy with LN dissection without use of neoadjuvant therapy, over a 16-year period. Most of the tumors were in the mid-esophagus, as expected (76%). The median number of four LN removed was relatively low compared with other series (range 1–24). The authors used a cutoff of six removed LN as the definition of "adequate" nodal dissection. The results showed that patients with six or more LN dissected had a higher rate of positive LN

Editorial about two papers: (1) "The Roles of Neoadjuvant Radiotherapy and Lymphadenectomy in the Treatment of Esophageal Adenocarcinoma" by Solomon et al. (ASO-2009-07-0832) and (2) "How Does the Number of Resected Lymph Nodes Influence TNM Staging and Prognosis for Esophageal Carcinoma?" by Hu et al. (ASO-2009-05-0621.R1).

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identified (46.9% versus 30.3%) and an improvement in overall survival that was statistically significant in pathologically node-negative (pN0) patients. This suggests that the survival benefit in patients with adequate LN dissection could be related to stage migration. Furthermore, there was no survival advantage in patients with pathologic LN metastasis relating to whether more or fewer than six lymph nodes were removed, suggesting that the lower survival for patients with inadequate lymphadenectomy may be a result of missed nodal involvement. It is interesting that, comparatively, the number of dissected LN is this study is lower than in most other series, yet it was able to demonstrate a difference in survival using a lower LN cutoff point.

In the second study, Solomon and colleagues performed a cancer registry analysis of the Surveillance, Epidemiology, and End Results (SEER) database, encompassing 4,224 patients with esophageal adenocarcinoma. The authors included patients treated also with radiation therapy to investigate whether multimodality therapy influenced the effect of lymphadenectomy in the treatment of esophageal cancer. The authors used a cutoff of more than 18 LN removed to classify lymphadenectomy as "adequate" based on previous available literature.[3] The authors report that 39% of patients had LN metastasis at time of surgery (pN1). Interestingly, 82.1% of patients had < 18 LN removed and were classified as receiving inadequate lymphadenectomy. The mean number of LN removed was 8.7. The majority of patients (55.8%) did not receive radiation therapy, and only 29% received neoadjuvant therapy in this cohort. The highest median survival time (MST) occurred in patients who received adequate lymphadenectomy and were pathologically node negative. They described that node-negative patients who received neoadjuvant radiation had worse survival outcome, but this may account for more advanced clinical stage and larger disease burden prior to therapy. The authors found that, in addition to adequate lymphadenectomy, use of radiation therapy (assumed to be chemoradiation) was an indicator of improved survival. Interestingly, in patients with pathologic LN metastasis who received neoadjuvant therapy, adequate lymphadenectomy was important to achieve improved survival, implying that adding another form of local therapy is not a substitute for adequate lymphadenectomy in this retrospective study.

These articles highlight several important issues in the surgical therapy of esophageal cancer. Certainly, it seems that, across the board, there is room for improvement in terms of lymph node yield during esophagectomy. As described in these two studies, the overall majority of patients did not undergo lymph node dissection that met the proposed goal of dissected nodes. However, the number of retrieved lymph nodes depends on multiple factors. From the surgeon's standpoint, the number of dissected lymph nodes will depend on the surgical approach (transhiatal versus transthoracic versus en bloc) and the number of dissected fields. Surgeons who perform their own nodal dissection of the specimen at the back table or submit individual packets of lymph nodes according to nodal stations will tend to obtain higher number of nodes, as noted in a recent multi-institutional trial.[6] From a pathological standpoint, the task of lymph node retrieval can be tedious, and often pathologists are too busy to perform an exhaustive search. At times this task is delegated to a junior pathology resident to be performed on a formalin-fixed specimen instead of a fresh specimen. Therefore, maximizing nodal retrieval for accurate staging is a collaborative effort between surgeons and pathologists. Institutional protocols can be implemented so that both surgeons and pathologists can maximize nodal yield. Cases where the nodal count seems low should prompt repeat examination of the specimen by an experienced pathologist to look for more LN, or review by the surgeon to determine whether technique modifications are warranted in subsequent cases.

Several questions remain. What is the optimal number of lymph nodes to classify an esophagectomy as adequate? Based on the available literature in both ESCC and adenocarcinoma, some authors recommend anywhere from 12 to 23 LN as the appropriate cutoff for "adequate" lymphadenectomy. The upcoming esophageal cancer staging in the AJCC staging manual recommends resection of as many lymph nodes as possible and that more nodes should be dissected with increasing pT stage (≥ 10 for T1; ≥ 20 for T2; and ≥ 30 for T3 and T4) based on worldwide data.[5] Certainly, sufficient nodal clearance should be performed to comfortably rule out missed nodal disease.

If nodal clearance is so important, should a more aggressive operation or adding a cervical field become standard for locally advanced esophageal cancer? Is the survival advantage of more radical operations a direct benefit or the effect of stage migration? In a prospective randomized trial comparing transhiatal (THE) versus transthoracic en bloc (TTE) esophagectomy, Hulscher and colleagues noted a much higher mean number of dissected LN (31 versus 16) and reported a trend towards improved survival, although it did not reach statistical significance.[7] Several surgical series have reported even higher number of dissected LN with improvement in survival even in patients with multiple LN metastases, but an increase in morbidity and possibly in mortality are frequently unavoidable in more radical operations.[8] Whether a more aggressive en bloc or routine three-field lymphadenectomy is a better esophageal cancer operation, or whether the number of dissected lymph nodes is the factor that impacts survival regardless of the technique, will require further investigation. Despite improved staging with more extensive lymphadenectomy and better locoregional control, the true impact on survival is still controversial, in part due to the effect of stage

migration and distant disease relapse. Further prospective studies will be needed to clarify this question.

As an alternative or in addition to more radical esophageal resections, many centers around the United States use neoadjuvant chemoradiation (CRT) for multimodality therapy for locally advanced (stage IIa–IVa) esophageal cancer, although the trials supporting this approach have many limitations. Despite this, this trimodality approach has dramatically reduced locoregional failures and has been shown to achieve pathological downstaging in a significant number of patients, resulting in improved prognosis. However, does the addition of CRT as another form of locoregional control impact the need for extended resections and a large LN retrieval? Pathologic response (pP) to neoadjuvant therapy has been shown to be a powerful prognostic indicator after esophagectomy. Patients with complete (P0) or near-complete (P1) response have been shown to have markedly improved prognosis. Swisher and colleagues have proposed another modification to the staging system to account for response to neoadjuvant therapy.[9] With the current data, it is unclear whether the same requirements in terms of number of LN for improved staging and survival apply in the setting of CRT. Most studies evaluating the survival effect of the number of resected LN exclude patients who received neoadjuvant therapy.

Given the results reported in these studies as well as others in the literature, a more standardized method of lymph node dissection for esophageal cancer is needed, as proposed in the new seventh edition of the AJCC TNM staging manual. From the surgeon's standpoint, regardless of the surgical approach or planned extent of lymphadenectomy, an effort should be made to resect as many regional LN as possible, as long as the resultant morbidity is acceptable. Collaboration between surgeons and pathologist to establish institutional protocols to maximize lymph node retrieval is essential. With more accurate staging and the application of a more robust staging system, future studies will be needed to further support the best approach to maximize locoregional control and survival in esophageal cancer.

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